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### The Quintet Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation

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**The Quintet Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation**

Rooshenas L<sup>1\*+</sup>, Scott LJ<sup>2+</sup>, Blazeby JM<sup>1</sup>, Rogers CA<sup>1,3</sup>, Tilling KM<sup>1</sup>, Husbands S<sup>1</sup>, Conefrey C<sup>1</sup>, Mills N<sup>1</sup>, Stein RC<sup>4</sup>, Metcalfe C<sup>1</sup>, Carr AJ<sup>5</sup>, Beard DJ<sup>5,6</sup>, Davis T<sup>7</sup>, Paramasivan S<sup>1</sup>, Jepson M<sup>1</sup>, Avery K<sup>1</sup>, Elliott D<sup>1</sup>, Wilson C<sup>1</sup>, Donovan JL<sup>1,2+</sup>. On behalf of the By-Band-Sleeve study group, CSAW study group, HAND-1 study group, Optima prelim study group, and the Romio feasibility study group (listed at end of manuscript).

<sup>1</sup> Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, Bristol, United Kingdom.

<sup>2</sup> NIHR Collaboration for Leadership in Applied Health Research and Care at University Hospitals Bristol NHS Foundation Trust

<sup>3</sup> Clinical Trials and Evaluation Unit, Bristol Royal Infirmary, School of Clinical Sciences, University of Bristol, Bristol, United Kingdom

<sup>4</sup> University College London Hospitals (UCLH), Biomedical Research Centre (BMC), University College London Hospitals, 1st Floor Central, 250 Euston Road, London NW1 2PG, UK.

<sup>5</sup> Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom.

<sup>6</sup> Royal College of Surgeons Surgical Intervention Trials Unit (SITU), University of Oxford, Oxford, United Kingdom.

<sup>7</sup> Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Derby Road, Nottingham, NG7 2UH, UK.

\*Corresponding author: [leila.rooshenas@bristol.ac.uk](mailto:leila.rooshenas@bristol.ac.uk); Leila Rooshenas, Tel: +44 (0) 11792 87327

+These authors made equal contributions

**Abstract**

**Objective:** To evaluate the impact of the Quintet Recruitment Intervention (QRI) on recruitment in challenging randomized controlled trials (RCTs) that have applied the intervention. The QRI aims to understand recruitment difficulties, and then implements 'QRI-actions' to address these as recruitment proceeds.

**Study Design and Setting:** A mixed-methods study, comprising: a) before-and-after comparisons of recruitment rates and numbers of patients approached, and b) qualitative case studies, including documentary analysis and interviews with RCT investigators.

**Results:** Five UK-based publicly-funded RCTs were included in the evaluation. All recruited to target. RCT2 and RCT5 both received up-front pre-recruitment training before the intervention was applied. RCT2 did not encounter recruitment issues and recruited above target from its outset. Recruitment difficulties, particularly communication issues, were identified and addressed through QRI-actions in RCTs 1, 3, 4 and 5. Randomization rates significantly improved post-QRI-action in RCTs 1,3, and 4. QRI-actions addressed issues with approaching eligible patients in RCTs 3 and 5, which both saw significant increases in patients approached. Trial investigators reported that the QRI had unearthed issues they had been unaware of, and reportedly changed their practices post QRI-action.

**Conclusion:** There is promising evidence to suggest the QRI can support recruitment to difficult RCTs. This needs to be substantiated with future controlled evaluations.

**Keywords:** Randomized Controlled Trial; Clinical trial; Recruitment; Training healthcare professionals; Qualitative research; Communication.

**Running title:** The Quintet Recruitment Intervention improved randomization rates and numbers of eligible patients approached in five challenging RCTs

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**What is new****Key findings**

- The Quintet Recruitment Intervention (QRI) supported five challenging randomized controlled trials in surgery/oncology to recruit to target. The QRI operated by first investigating the sources of recruitment difficulty in each RCT, and then implementing tailored 'QRI-actions' to address the issues as recruitment proceeded.
- Four of the five RCTs encountered recruitment challenges, underpinned by difficulties in communicating the trial to potential participants and issues around approaching eligible patients. These issues were addressed through QRI-actions delivered as the RCTs were recruiting.
- Randomization rates significantly improved post QRI-action in three trials that encountered communication difficulties. There was no significant difference in two RCTs, which both recruited above target from their outset and had received previous QRI support. Two trials that received QRI actions designed to address issues around approaching patients saw significant improvements in the numbers of patients approached per site/month.

**What this adds to what is known**

- There is a growing body of empirical research devoted to explaining why recruitment can be challenging, but a dearth of effective solutions. Numerous systematic reviews have repeatedly highlighted the paucity of broadly applicable, effective strategies to improve trial recruitment. This initial evaluation suggests that the QRI can effectively identify and address recruitment issues, leading to improvements in recruitment in a range of RCTs.

**What is the implication, what should change now**

- This evidence provides a platform for trialists to consider adopting the QRI (or similar approaches) in their RCTs, particularly if recruitment issues are anticipated. Future controlled evaluations of the QRI are needed to build upon this promising evidence.

**1. Introduction**

High quality evidence about treatment effectiveness is crucial for improving patient outcomes and promoting judicious use of resources. Well-conducted randomized controlled trials (RCTs) can provide this evidence, but one of the biggest threats to an RCT's success is sub-optimal recruitment. This can compromise a trial's statistical power, delay implementation of findings, and lead to costly extensions or early closure.[1,2] Various guidance and tools (e.g. PRECIS-2) are now available to support trial design and planning,[3, 4] but only half of RCTs meet their recruitment targets,[5] and recruitment issues remain the top reason for premature closure.[1, 6] The threat of recruitment difficulties can also discourage important RCTs from being attempted.

There is a growing body of empirical research devoted to understanding RCT recruitment issues, but a paucity of effective solutions.[7-10] The little work that has been conducted has predominantly focused on lessons learnt from previous RCTs.[10] Promising initiatives, such as the MRC 'Start' programme and the clinical trials transformation initiative (CTTI), aim to empirically test interventions designed to support recruitment,[11, 12] but interventions evaluated to date have had a narrow field of application or emerged as ineffective.[8] There remains an urgent need for widely

applicable interventions to facilitate RCT recruitment [7, 8], particularly for challenging RCTs, such as those comparing very different approaches to managing life-changing conditions.

The QuinteT (Qualitative Research Integrated into Trials) Recruitment Intervention (QRI) was designed to optimise RCT recruitment.[13] It evolved over the course of two decades since its inception in the ProtecT study – a challenging RCT that randomized men to surgery, radiotherapy, or monitoring for localised prostate cancer.[14, 15] Rather than relying on fixed strategies, the QRI delivers tailored solutions to improve recruitment, based on a detailed understanding of trial-specific challenges. The intervention focuses on how trial information is communicated to potential participants, and seeks to identify and address other factors that may undermine recruitment (e.g. difficulties approaching potential participants). The QRI has been implemented in a growing number of challenging RCTs,[16-20] some of which have now completed and reported.[21-23]

The aim of this study was to evaluate the impact of the QRI on RCT recruitment. We undertook a mixed-methods evaluation of all main and pilot RCTs that have integrated the intervention and completed (or stopped) recruitment to date. Our primary objective was to investigate the impact of the QRI on recruitment rates. Secondary objectives were to explore the QRI's likely mechanisms of action and identify opportunities for its refinement.

## **2. Materials and Methods**

### **2.1. Overview of the QRI**

The QRI is designed to be integrated with an RCT's recruitment plans. It aims to rapidly understand recruitment issues, and then implement solutions to address these whilst recruitment is underway. This is achieved through two iterative phases.[13] In brief:

- Phase 1 is a rapid investigation of the RCT's recruitment processes using four core data collection processes: 1) audio-recording appointments where recruiters discuss the trial with potential participants; 2) interviews with recruiters and trial management group (TMG) members; 3) mapping eligibility and recruitment pathways; and 4) scrutinising trial documentation. The findings from each source are triangulated to determine the key areas of recruitment difficulty and fed back to the Chief Investigator and TMG.
- Phase 2 involves designing and implementing a 'plan of action' to address recruitment difficulties. The plan comprises one or more 'QRI-actions', typically including: confidential feedback for recruiters who audio-record their appointments, group feedback/training, written 'Tips and Guidance', and changes to trial documentation and processes (e.g. patient information leaflets, recruitment pathways). QRI-actions are designed and delivered collaboratively by the QRI researcher(s) and the TMG.

### **2.2. Study design and sampling**

A mixed-methods evaluation of the QRI was undertaken, comprising a quantitative before-and-after comparison of recruitment rates and a qualitative case study analysis of each RCT's recruitment process.

RCTs eligible for inclusion needed to have integrated the full QRI and be closed to recruitment (or have completed pilot/feasibility stages). All RCTs that had collaborated with the QuinteT team between 2005-2017 were assessed, and fulfilment (or not) of each QRI component was recorded by LR and cross-checked by researchers who worked on each RCT (See Supplementary Information 1).

### **2.3 Data collection and analysis**

### 2.3.1 Documentary analysis

The documentary analysis was conducted first, to produce an overview of the recruitment issues identified through the QRI and the QRI-actions implemented to address these. Each eligible RCT's protocol, funding application, and papers/reports were consulted for information about the trial and QRI (see Supplementary Information 2).

### 2.3.2 Quantitative analysis

Recruitment logs maintained by clinical trials units (CTUs) recorded the number of eligible patients approached per month, and the number of those who went on to be randomized, for each site within each RCT. Site-specific data were not available for RCT4, so total monthly recruitment figures were used instead. Data from only one of the two sites in RCT2 were included because recruitment log information was not available for the other site. All RCTs recorded the number of patients randomized per month, apart from RCT3, which referred to the 'number of patients consented'; we therefore used 'consent' as a surrogate for randomization for this trial.

'QRI-actions' were defined as any initiatives to optimise recruitment that had been informed by phase 1 QRI findings, including study-wide actions (e.g. dissemination of written guidance on how to explain the trial), or site-specific activities (e.g. feedback to a recruiter). As the timing and nature of the first QRI-action could differ across sites in a given RCT, patients approached in the time up to and including the month of the first 'QRI-action' (in their trial and site) were considered part of the 'pre-intervention' period; patients approached in any month after were part of the 'post-intervention' period. In the absence of site-specific data for RCT4, we conservatively assumed that all QRI-actions impacted all sites.

The analysis was conducted by an independent statistician (LJS) blind to the RCTs' identities. The analysis plan was determined before accessing the data. All statistical analyses were performed in Stata 15.1.

Analysis 1 investigated randomization success (whether a patient who was eligible and approached went on to be randomized). The association between pre/post intervention and randomization success was analysed using a mixed effects logistic regression model, with pre/post intervention and trial fitted as fixed effects, and site as a random effect. Results are presented as odds ratios (OR) with associated confidence intervals (CI). Whether the effect of pre/post intervention differed by trial was investigated by fitting a 'pre/post intervention by trial' interaction term in the model; if the interaction was significant at the  $p=0.05$  level then results were presented by trial rather than overall.

Analysis 2 examined the number of patients approached per site in the pre and post intervention periods. The association between pre/post intervention and number of patients approached per site/month was analysed using a mixed Poisson regression model, with pre/post intervention and trial fitted as fixed effects, adjusting for the number of months of recruitment at a site as the exposure, and site fitted as a random effect. Results were presented as incident rate ratios (IRR) with associated CIs. Again, results were presented by trial if the pre/post intervention by trial interaction was significant at the  $p=0.05$  level.

### 2.3.3 Qualitative analysis

Semi-structured interviews were conducted to investigate how the QRI had been implemented in each RCT as a means of triangulating the documentary analysis findings. Interviews also explored trialists' perceptions of the strengths and limitations of the QRI. A key informant sampling approach



was used, where RCT TMG members who had been involved in recruitment were identified and invited (via email) to participate. Interviews were conducted between November 2016- August 2017 via telephone or in person, and audio-recorded with permission. A topic guide was used to consistently cover topics aligned with the objectives (Supplementary Information 3). Written consent had already been obtained through the QRIs, and interviewers (LR and SH) verbally confirmed individuals were happy to participate.

Interviews were transcribed verbatim and analysed through constant comparative approaches adopted from Grounded Theory.[24, 25] This was an iterative process, involving line-by-line coding of data and arrangement of codes into themes and sub-themes as new data were obtained and previously coded transcripts were revisited. NVivo (V10, QSR International) was used to organise the data. Interviews were analysed by LR, with a subset double-coded by a researcher who had not worked on any of the trials (CC). 'Negative' cases that appeared to contradict emerging themes were sought and presented in the findings where apparent.

### **3. Results**

Thirty RCTs were considered for inclusion, with start dates spanning 2005-2017. Fifteen RCTs were excluded because they had not finished recruitment at the time of the evaluation, and 10 were ineligible because they did not implement the full QRI (see Supplementary Information 4 for reasons why).

Five RCTs were included in the evaluation. All were pragmatic, publicly-funded trials in UK secondary care settings, spanning different clinical specialties and comparing very different treatments, including less/no treatment (Table 1). Four had integrated the QRI from the outset due to anticipated recruitment challenges, and one RCT integrated the QRI partway through, in response to recruitment difficulties. Figure 1 shows the timeline for each RCT, including when the QRI started (initiation of Phase 1), and when QRI-actions started to be implemented (Phase 2). The timing of the first QRI-action ranged from month 3 to month 14 of the RCT's recruitment period.

Two trials (RCT2 and RCT5) had received support from QuinteT before recruitment started. RCT5 received up-front training/guidance, including a generic presentation on recruitment challenges/solutions at the trial's launch, customised 'Tips and guidance' documents for explaining the RCT, refinements to patient-facing literature, and some recruiters had attended a generic QuinteT recruitment workshop.[26] RCT2 recruiters had been exposed to QRI feedback in a previous trial.[27] This prior support did not fulfil the definition of 'QRI-actions' because activities were not informed by trial-specific investigation of recruitment issues. Therefore, the periods up to the first 'QRI-action' were still considered 'pre-intervention' in these trials.

#### **3.1. Recruitment outcomes**

All RCTs successfully recruited their target samples. Four achieved this on time or earlier than planned, without opening additional sites (RCTs 1,2,3, and 5). RCT4, which integrated the QRI partway through its funded period, had an extension and opened eight additional sites.

##### **3.1.1. Analysis 1: changes in randomization success**

Based on pooled data across the RCTs, 307/783 (39%) of approached eligible patients were randomized before the first QRI-action, compared with 582/1160 (50.2%) after (Table 2). The effect of pre/post intervention differed for the individual RCTs (pre/post intervention by trial interaction  $p=0.018$ ), and so each trial was considered individually in the model (Figure 2, panel 1). Randomization success significantly improved post-intervention for RCT1 (OR 4.55, 95% CI 1.72-

12.02), RCT3 (OR 1.54, 95% CI 1.12-2.12) and RCT4 (OR 2.66 (95% CI 1.90-3.72). There was no evidence of a difference in RCT2 (OR 1.68, 95% CI 0.58-4.82) and RCT5 (OR 1.01, 95% CI 0.52-1.97).

### **3.1.2. Analysis 2: changes in the number of patients approached per site/month**

The pooled data across all RCTs showed that 1.7 patients were approached per site/month in the pre-intervention periods, compared with 1.3 patients per site/month in the post-intervention periods (Table 3). Considering the trials separately (pre/post intervention by trial interaction  $p < 0.001$ ; Figure 2, panel 2), the number of patients approached significantly decreased post-intervention in RCT4 (IRR 0.43, 95% CI 0.37-0.51), did not change in RCT1 (IRR 1.10, 95% CI 0.79-1.53) and RCT2 (IRR 1.04, 95% CI 0.62-1.75), and showed a significant improvement in RCT3 (IRR 1.17, 95% CI 1.01-1.36) and RCT5 (IRR 1.66, 95% CI 1.21-2.28).

## **3.2 Recruitment obstacles**

Table 4 lists the challenges identified in each RCT. Recruitment issues fell under two categories:

### **3.2.1 Issues relating to communicating the trial to eligible patients**

Recruitment to most trials (RCTs 1, 3, 4, and 5) was undermined through difficulties in explaining the RCT to potential participants ("communication issues"). These included equipoise issues, apparent through recruiters' difficulties in articulating uncertainty, and imbalanced descriptions of the trial arms (where particular treatments were conveyed as being superior or more appropriate). Difficulties addressing patient preferences for particular treatments/approaches were also common, but most problematic in RCT1, where the majority (>87%) of patients approached declined the trial in favour of a preferred treatment. Audio-recorded appointments revealed a tendency for recruiters to elicit patients' preferences at the start of the consultation, and then accept these without discussing the RCT.

More specific issues arose in individual trials, such as difficulties in articulating trial designs. For example, RCT3 randomized patients to routine treatment versus 'test-directed' treatment, whereby patients received a test that was hypothesised to inform their optimal treatment (i.e. "personalised treatment"). Patients sometimes found it difficult to comprehend the distinction between randomization and 'testing', both of which played a role in determining final treatment prescribed. Design-related issues also arose in RCT4, where surgical recruiters encountered difficulties in articulating placebo and non-surgical arms.

As an exception, RCT2 revealed few communication issues to address in the pre-intervention stage; QRI-actions therefore encouraged recruiters to continue their practices, with some suggestions for additional information provision geared towards better informing patients.

### **3.2.2 Issues pertaining to the number of patients approached**

Recruitment pathways varied from one site to another and were inefficient in some sites, as in RCT5. Interviews with recruiters from RCT5 and RCT3 also indicated that some recruiters felt uncomfortable offering the trial to eligible patients who they felt would be more appropriate for one treatment over another; this appeared to restrict the numbers of eligible patients approached.

## **3.3 QRI-actions to optimise recruitment**

The QRI-actions implemented in each RCT are shown in Table 4. Feedback on recruiters' communication practices was at the heart of each trial's 'plan of action' to optimise recruitment, delivered to individuals or groups of recruiters (e.g. a single centre or multiple centres). Feedback



used anonymised extracts from recruitment appointments/interviews to illuminate difficulties and potential solutions, focusing on issues around equipoise communication, articulation of RCT designs, and management of patient preferences. Group feedback sessions offered opportunities for peer-to-peer discussion; individual feedback offered more specific advice, bespoke to a recruiter's practices.

Study-wide QRI-actions to address communication issues were delivered in all RCTs through trial-specific 'Tips and Guidance' documents. These included recommendations for structuring consultations and explaining common concepts (e.g. 'randomization'). Changes to patient-facing documentation were also implemented in some RCTs with a view to conveying equipoise and trial design more clearly (e.g. RCT3).

Issues around approaching patients were addressed by reviewing summaries of screening logs and exploring cases where eligible patients had not been approached. In RCT3, hypothetical vignettes were used to prompt discussion around contentious aspects of the eligibility criteria to encourage peer-to-peer discussion. The intention here was to enable recruiters who were less comfortable approaching patients with certain characteristics to gain reassurance from peers who were more comfortable.<sup>(17)</sup> Scrutiny of patient pathways and suggestions for refining how patients were identified/approached were also discussed in site-specific feedback sessions in RCT5.

### **3.4 Overall impact of QRI-actions**

Randomization success improved in RCTs 1,3, and 4, all of which appeared to be compromised by communication issues. Communication issues were also apparent in RCT5, but there was no difference in randomization success (although the trial recruited above target throughout its duration). There was also no significant improvement in randomization success in RCT2, although the documentary analysis indicated that QRI-actions encouraged recruiters to maintain their current successful practices. RCT2 and RCT5 recruited above target throughout, and both had been exposed to prior QuinteT training.

The numbers of patients approached per site/month improved post-intervention in RCTs 3 and 5, in line with documented strategies designed to address issues around approaching patients. No significant improvements were observed in the other RCTs, but there were no QRI-actions that specifically targeted approach issues. The number of eligible patients approached per site/month significantly decreased in RCT4. Informal correspondence with the TMG indicated that fewer eligible patients were being identified in the later stages of this trial, reportedly due to depletion of prevalent cases. The qualitative interviews also indicated that the new centres opened during the post-intervention period did not engage as well as original centres, which diluted the number of patients approached per site/month.

### **3.5 Trialists' perspectives on the QRI**

Seven trial investigators representing all five RCTs participated in interviews. Their accounts of the QRI activities generally complemented the documentary data. The one exception to this was RCT2. Although the documentation indicated that the mandatory components of the QRI had been conducted, interviews suggested that the QRI was not fully implemented as it was not deemed necessary (following observation of successful recruitment trends). RCT2 did not have a dedicated QRI researcher, and the QRI activities were not conducted intensively. This was corroborated by researchers who contributed to RCT2's QRI, both of whom questioned whether RCT2 was eligible for the evaluation. Informants' accounts from other trials indicated that the QRI had been delivered as reported in the documentary sources.

Trial investigators were forthright about the difficulties of quantifying the impact of the QRI but most felt that QRI-actions translated into improved recruitment (web appendix 1). Most discussed how the QRI had introduced them to sources of difficulty that they had previously been unaware of, and those with direct experience of recruiting gave specific examples of how the QRI had changed their discussions with patients. Individual/group feedback and written guidance were thought to have catalysed these changes:

*Investigator 4: In the very early days I was a very poor recruiter. [...]. .... And actually I learnt from [the QRI], and the work [QRI researcher] did. Because towards the end I was much more successful, and I had really started to follow the guidance in the Tips document. And I think it was extremely useful.*

*Investigator 5: The problem-solving nature of it was just a different level of consideration on what the issues were. [...] No question – no question [in response to being asked if they felt the QRI had an impact]. So this language that I'm speaking now is a direct result of that thinking. I don't think we'd delineated it to the same extent then at all. It seems very straight forward and obvious now [...] – but this was a completely different world to us. We were just clinicians in a clinic, saying "there's a trial here [...] - do you want to go in it?" [...] I expected, in the beginning, I'll be honest – I expected "We'll do all this talk and it won't make a difference" – but it did make a difference.*

One informant stood apart, having indicated that the feedback of QRI findings had not been 'surprising', although still mentioned specific issues that had compromised recruitment in sites other than their own:

*Investigator 9: There's nothing that came as a surprise, but I think it was good. I mean, I think it had an impact. I think recruitment suddenly improved somewhere else.*

*Interviewer: In what way do you think?*

*Investigator 9: Well, I think people realised that they were overselling [treatment x] and didn't realise. [Later] But if we get [another study], I think it's very important to have it [QRI] at centres.*

Several informants highlighted the necessity for Chief Investigators, CTUs and recruiters to engage with the QRI, and for its processes to be integrated with the trial to facilitate success:

*Investigator 5: The key thing for me was getting the chief investigator and the team around them engaged with it. It will never work if the chief investigator doesn't get it.*

Some questioned whether QRI-actions had reached all sites, particularly those less engaged with the RCT, but there were also suggestions that feedback/training was unlikely to be restricted to sites the QRI team directly worked with (web appendix 2). When asked to summarise their impressions of what the QRI entailed, most emphasised the feedback/training elements, informed by audio-recordings of recruiters' actual practices. Informants tended to discuss the QRI as a 'complex intervention', hesitating to pin-point any one aspect that was more effective than another:

*Investigator 5: The whole is greater than the sum of its parts.*

*Investigator 2: I wouldn't want to put it down to one particular thing. I think it was a combination of things that had an effect. [...] I think it's much better if it's integrated into the whole structure.*

## 4 Discussion

This paper reports the first empirical evaluation of the QRI – an intervention designed to optimise recruitment in challenging RCTs. The QRI's impact on recruitment was examined in five RCTs from oncology and surgical specialties. The QRI identified issues that appeared to undermine recruitment to most of the RCTs, particularly in relation to how the RCT was communicated to patients. QRI-actions sought to address these difficulties through feedback/training, dissemination of written guidance, and changes to patient-facing documentation. There was evidence of improvement in randomization success post-intervention in three RCTs; the two RCTs that did not see an improvement both recruited above target throughout their durations (and had received up-front/prior QRI recruitment training). The QRI also identified issues around approaching eligible patients in some RCTs, resulting in QRI-actions designed to improve opportunities for approaching patients. The numbers of eligible patients approached per site/month significantly increased in two trials that specifically implemented these QRI-actions. The number of patients approached did not change, or significantly decreased, in the post-intervention periods of other RCTs without these QRI-actions. Trialists perceived a change in recruitment practices after QRI-actions, particularly in relation to how they communicated with patients, with most reporting that the QRI had unearthed issues they had not previously considered. Full integration of the QRI into the RCTs, with support from chief investigators and CTUs, was deemed integral to the QRI's success.

The study had several limitations. We cannot establish cause-effect relationships between QRI-actions and recruitment and cannot account for other factors that might have explained changes observed. To minimise these limitations, we examined pre/post intervention periods at the level of each site within each trial, rather than defining blanket pre/post intervention cut-off periods at the overall trial level. The improvements in randomization success in multiple RCTs supports the notion that the QRI-actions were genuinely influencing and changing recruitment, although it is possible that recruiters naturally improved their practices over time. The changes observed are unlikely to be due to spontaneous improvements, given that the QRI identified issues that recruiters were not aware of. Furthermore, QRI-actions (and improvements) occurred more than one year into the recruitment periods of some RCTs, by which point recruiters' practices had likely stabilised.

The evaluation was only undertaken with five UK RCTs, and thus would be strengthened by inclusion of more trials spanning a diversity of settings. There were also limitations in the quality and completeness of data available, leading to several *a priori* assumptions. We assumed that QRI-actions affected all recruiters in any given site, and that all sites and recruiters had been exposed to every 'study-wide' QRI-action (e.g. 'Tips and Guidance' documents). The large RCTs had many centres that never directly engaged with the QRI, but we counted their recruitment activity as 'post-intervention' following any study-wide QRI-actions. These limitations are likely to have resulted in a more conservative estimate of QRI impact, as recruiters not truly exposed to QRI-actions may have diluted the 'post-intervention' effect. The qualitative evaluation was limited by the possibility that informants' responses were influenced by knowledge that the interviewer was affiliated with QRI researchers who worked on their trials. As such, the interviews primarily focused on examining how the QRI operated in each RCT, rather than trialists' perceived value of the QRI.

Strengths of the study included the use of mixed-methods, which allowed for a detailed understanding of whether (and how) the QRI was likely to have impacted recruitment. The independent documentary analysis and qualitative interviews triangulated our understanding of the potential mechanisms of change in each RCT, and thus plausibility of effect.

The QRI has previously been recognised as a promising intervention, in a field that is largely devoid of effective solutions to addressing recruitment issues.[28-30] When faced with the pressures of improving recruitment, trialists often try multiple strategies concurrently, making evaluation difficult. Randomised evaluations have tended to test relatively simple interventions, such as altering patient information materials or arranging site visits.[31-36] These have largely been shown to have little impact on recruitment, although increasing patients' knowledge about the clinical condition, telephone reminders, monetary incentives, and 'opt out' processes can be effective.[7, 8] However, most of these strategies are unlikely to improve recruitment in complex trials involving life-changing conditions or very different interventions, as considered in this evaluation.

The extensive literature on reasons for poor recruitment supports plausible mechanisms of action for the QRI. Recruiters can experience complex intellectual challenges, relating to struggles with equipoise, role conflict, and concerns about their relationships with patients.[37, 38, 39] Retrospective analyses of reasons for trial failure have also indicated that most issues are "preventable", with recruiters' and patients' pre-conceptions about treatments frequently underpinning reasons for discontinuation.[40] The QRI recognises that recruiters' attitudes, beliefs, and skills can undermine recruitment at several stages— from identifying eligible patients, through to approaching them and presenting the option of trial participation. Although not exclusively a 'recruiter-targeted' intervention, most QRI-actions are geared towards altering recruiters' practices through guidance and feedback. Other 'recruiter-targeted' interventions have taken the form of one-off training,[41] although those that have shown positive effects have been context-specific.[42, 43] Similar to the QRI, one potentially transferable initiative trained recruiters to elicit and respond to patients' views about trial participation; this appeared to be associated with recruitment success when evaluated in a single trial.[44] The theoretical and empirical literature on clinicians' learning underlines the importance of specific, pre-planned, data-driven feedback.[45, 46] In particular, cognitive learning theory proposes that individuals learn by organising and relating new information to existing knowledge, with feedback presented as one way of achieving this.[47]

Application of the QRI to a growing number of RCTs has provided opportunities to identify common recruitment issues [48, 37, 38, 49] and design pre-emptive training.[26] RCTs that have most recently integrated the QRI have included up-front training/guidance, as in RCT5 which did not see a significant improvement in randomization success, although numbers of patients approached per site/month increased following QRI-actions designed to address issues around approaching patients. It is possible that the up-front training may have enhanced recruitment in the 'pre-intervention' period, or RCT5 might have recruited well without the QRI. RCT2, which had prior exposure to QRI-actions, also recruited above target with no notable issues. Further work is required to investigate the role of up-front generic training versus responsive feedback, and any sustainable effects of QRI-feedback. Pre-recruitment training might address some generic issues (e.g. suggestions for explaining randomization) but is unlikely to address more complex challenges such as equipoise communication, which can be disrupted by trial-specific contextual factors.

Future evaluations of the QRI need to include individual recruiter-level data. Examination of the cost-effectiveness of the QRI would also be valuable, given that the QRI requires time and resources (though likely to be small relative to the costs associated with sub-optimal recruitment),[13] and should consider the transferability of QRI feedback/training to other RCTs. Ideally, future evaluations of the QRI should incorporate randomization. Randomizing sites in a given RCT to receive the QRI (or no QRI) would be challenging due to the 'ripple effect' of QRI-actions and cross-site contamination. Randomization could occur at the RCT level, although this would be practically difficult and require

large numbers of trials. Despite these complications, the promising evidence needs to be substantiated by future more robust evaluations of the QRI and its components.

#### **4.1 Conclusion**

The QRI supported recruitment in five challenging RCTs, all of which successfully achieved their recruitment targets. There was strong evidence that QRI-actions improved randomization success in the RCTs, with the exception of two RCTs that had received pre-recruitment QRI training/support, which recruited well from the outset. Improvement in the number of eligible patients approached was also apparent in two RCTs where these issues were specifically addressed. Tailored feedback to recruiters was at the heart of the QRI-actions, and was perceived by recruiters to have had an impact on their practices. Whilst more robust evaluation is required, there is evidence that the QRI has a positive effect on recruitment in a range of RCTs.

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### Author contributions

LR and JLD had the original idea to develop this manuscript. LR designed the qualitative aspects of the study (documentary analysis, interviews) and LJS designed and analyzed the quantitative evaluation. JLD leads the QuinteT programme of research and gained funding to support it in collaboration with the CIs and co-investigators of the RCTs [JMB, CAR, RCS, CM, DJB, AJC, TD, NM]. LR developed the first draft with support from LJS and JLD. LR, SH, NM, SP, MJ, and KA helped with data acquisition. CAR, CC, and KMT contributed to data analysis. All authors commented on previous drafts and approved the final manuscript. LR, LJS and JLD are guarantors.

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### Details of ethical approval:

Ethical approval to conduct the qualitative aspects of this research was secured through each individual RCT. The research ethics committee names and reference numbers for approval for each RCT are as follows (in alphabetical order):

*By-Band-Sleeve: South West - Frenchay Research Ethics Committee (11/SW/0248), December 2011.*

*CSAW: South Central–Oxford B Research Ethics Committee (12/SC/0028), February 2012.*

*Hand-1: East Midlands – Derby Research Ethics Committee (Ref: 15/EM/0197)*

*Optima prelim– South East Coast Surrey Research Ethics Committee (12/LO/0515), June 2012*

*Romio feasibility study– National Research Ethics Committee South West - Frenchay, (ref: 12/SW/0161)*

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Table 1: Details of the RCTs included in the evaluation

RCT identifier	Feasibility or Main study	Clinical speciality	Trials arms	Number of sites	Duration of recruitment period (months)	Point of QRI integration
RCT1 (ISRCTN007 86323)	Feasibility (internal pilot)	Bariatric surgery	Surgical procedure A vs Surgical procedure B	2	20	Outset
RCT2 (ISRCTN590 36820)	Feasibility (external pilot)	Surgery for esophageal cancer	Surgical procedure A vs Surgical procedure B	2*	12	Outset
RCT3 (ISRCTN424 00492)	Feasibility (external pilot)	Oncology (breast cancer)	Drug treatment vs 'Test-directed' drug treatment	35	21	Incorporated into the RCT protocol from the outset, but began on month 8 of recruitment period.
RCT4 (ISRCTN 33864128)	Main	Orthopaedic surgery (shoulders)	Assessment/monitoring vs Surgery vs Placebo surgery	32	34	Incorporated into the RCT protocol partway through the recruitment period; began in month 8.
RCT5 (ISRCTN111 64292)	Feasibility	Orthopaedic surgery (hands)	Surgical procedure A vs Surgical procedure B	3	10	Outset
* Although the RCT took place across two sites, only one of these provided screening log data, and thus only one site was included in this evaluation.						

**Table 2: Numbers and proportions of eligible and approached (E&A) patients randomised in the pre-intervention period (before the first QRI-action) and post-intervention period, shown for all trials combined and each individual trial**

		Number of E&A patients (N)	Number of randomised patients (n)	Proportion of E&A patients randomised (n/N)
<b>All RCTs combined</b>	<b>Pre-intervention period</b>	<b>783</b>	<b>307</b>	<b>39.2%</b>
	<b>Post-intervention period</b>	<b>1160</b>	<b>582</b>	<b>50.2%</b>
	<i>Period following:</i> 1-2 QRI-actions	518	246	47.5%
	3-4 QRI-actions	237	117	49.4%
	5+ QRI-actions	405	219	54.1%
<b>RCT1</b>	<b>Pre-intervention period</b>	<b>40</b>	<b>5</b>	<b>12.5%</b>
	<b>Post-intervention period</b>	<b>304</b>	<b>119</b>	<b>39.1%</b>
	<i>Period following:</i> 1-2 QRI-actions	120	47	39.2%
	3-4 QRI-actions	61	24	39.3%
	5+ QRI-actions	123	48	39.0%
<b>RCT2</b>	<b>Pre-intervention period</b>	<b>55</b>	<b>22</b>	<b>40.0%</b>
	<b>Post-intervention period</b>	<b>19</b>	<b>10</b>	<b>52.6%</b>
	<i>Period following:</i> 1-2 QRI-actions	13	8	61.5%
	3-4 QRI-actions	6	2	33.3%
	5+ QRI-actions	-	-	-
<b>RCT3</b>	<b>Pre-intervention period</b>	<b>382</b>	<b>164</b>	<b>42.9%</b>
	<b>Post-intervention period</b>	<b>363</b>	<b>186</b>	<b>51.2%</b>
	<i>Period following:</i> 1-2 QRI-actions	260	127	48.8%
	3-4 QRI-actions	103	59	57.3%
	5+ QRI-actions	-	-	-
<b>RCT4</b>	<b>Pre-intervention period</b>	<b>230</b>	<b>80</b>	<b>34.8%</b>
	<b>Post-intervention period</b>	<b>396</b>	<b>232</b>	<b>58.6%</b>
	<i>Period following:</i> 1-2 QRI-actions	49	29	59.2%
	3-4 QRI-actions	65	32	49.2%
	5+ QRI-actions	282	171	60.6%
<b>RCT5</b>	<b>Pre-intervention period</b>	<b>76</b>	<b>36</b>	<b>47.4%</b>
	<b>Post-intervention period</b>	<b>78</b>	<b>35</b>	<b>44.9%</b>
	<i>Period following:</i> 1-2 QRI-actions	76	35	46.1%
	3-4 QRI-actions	2	0	0%
	5+ QRI-actions	-	-	-

E&A=eligible and approached

**Table 3: Average number of patients eligible & approached (E&A) per site per month, in the pre-intervention and post-intervention period for each RCT, and for all RCTs combined.**

		Number of site months	Number of E&A patients	Average number of E&A patients (per site per month)
All RCTs combined	Pre-intervention period	453	783	1.7
	Post-intervention period	900	1160	1.3
RCT1	Pre-intervention period	4	40	10
	Post-intervention period	33	304	9.2
RCT2 <sup>a</sup>	Pre-intervention period	9	55	6.1
	Post-intervention period	3	19	6.3
RCT3	Pre-intervention period	265	382	1.4
	Post-intervention period	227	363	1.6
RCT4	Pre-intervention period	157	230	1.5
	Post-intervention period	626	396	0.6
RCT5	Pre-intervention period	18	76	4.2
	Post-intervention period	11	78	7.1

E&A=eligible and approached; <sup>a</sup>Site data available from one of the 2 recruiting sites;



**Table 4: Summary of key sources of recruitment difficulty based on Phase 1 findings, and timing/type of QRI-actions to address difficulties**

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RCT identifier	Key sources of recruitment difficulties to emerge from Phase 1 investigation	Timing (recruitment month) and type of Phase 2 QRI-actions
<b>RCT1</b>	<p>1) Difficulties integrating the RCT into existing clinical service:</p> <ul style="list-style-type: none"> <li>a) Complex recruitment pathways (from point of identifying eligible patients, to the recruitment appointment)</li> <li>b) Structure of consultations was often not conducive to explaining the RCT rationale; RCT participation was not presented as a viable option.</li> </ul> <p>2) Difficulties conveying equipoise when describing trial arms to patients</p> <p>3) Tendency to accept patient preferences, without exploration</p> <p>4) Difficulties articulating and explaining trial concepts (e.g. 'randomisation')</p>	<ul style="list-style-type: none"> <li>• Month 3: individual feedback for Site 1</li> <li>• Month 4: group feedback for Site 1</li> <li>• Month 7: individual feedback for Site 1</li> <li>• Month 8: group feedback for Site 1</li> <li>• Month 9: individual feedback for Site 2</li> <li>• Month 11: individual feedback for Site 1</li> <li>• Month 13: individual feedback for Site 2</li> <li>• Month 14: individual feedback for Site 2</li> <li>• Month 16: 'Tips and guidance' document circulated to all sites</li> <li>• Month 18: individual feedback for Site 1</li> <li>• Month 18: Research nurse training event (both sites)</li> </ul>
<b>RCT2</b>	<p>Recruitment was perceived to be progressing well throughout, and recruiters were encouraged to continue their practices. Additional tips were provided in relation to:</p> <ul style="list-style-type: none"> <li>1) Conveying equipoise during recruitment appointments (when describing trial arms)</li> <li>2) Explaining trial concepts (e.g. 'randomisation' and 'blinding')</li> <li>3) Addressing patient preferences</li> </ul>	<ul style="list-style-type: none"> <li>• Month 8: Group feedback for Site 2</li> <li>• Month 9: Individual feedback for 2 recruiters in Site 1</li> <li>• Month 11: Group feedback for Site 1 (clinicians)</li> <li>• Month 11: 'Tips and Guidance' document circulated to all sites</li> </ul>
<b>RCT3</b>	<ul style="list-style-type: none"> <li>1) Clinicians' discomfort approaching the full spectrum of eligible patients (clinicians' individual sense of equipoise).</li> <li>2) Clinicians' and research nurses' discomfort around introducing the study, based on assumptions that patients would not be able to process the offer of trial participation.</li> <li>3) Structure of consultations was not conducive to explaining the RCT rationale; RCT participation was not presented as a viable option.</li> <li>4) Difficulties articulating uncertainty and conveying equipoise during recruitment appointments</li> <li>5) Difficulties explaining the trial design clearly</li> <li>6) Tendency to accept patient preferences, without exploration</li> <li>7) Difficulties articulating and explaining trial</li> </ul>	<ul style="list-style-type: none"> <li>• Month 14: 'Tips and Guidance' document circulated to all sites</li> <li>• Month 15: Edited patient information leaflet circulated to all sites</li> <li>• Month 15: Group feedback presented to region 1 (attended by five sites).</li> <li>• Month 17: Group feedback presented to region 2 sites, with discussion of hypothetical vignettes (attended by 7 sites)</li> <li>• Month 18: Individual feedback provided for recruiter from one site</li> <li>• Month 19: Individual feedback provided for recruiters from 3 sites</li> <li>• Month 19: Group feedback to two sites.</li> </ul>

	concepts (e.g. 'randomisation' and 'blinding')	
	ACCEPTED MANUSCRIPT	
<b>RCT4</b>	<p>1) Difficulties articulating and explaining the trial treatments/management approaches</p> <p>2) Difficulties conveying equipoise during recruitment appointments (when describing trial arms)</p> <p>3) Difficulties explaining the trial design</p> <p>4) Tendency to accept patient preferences, without exploration</p>	<ul style="list-style-type: none"> <li>• Month 13: individual feedback</li> <li>• Month 14: individual feedback</li> <li>• Month 15: 'Tips and Guidance' in study-wide newsletter</li> <li>• Month 16: Study-wide group feedback, attended by 15 sites</li> <li>• Month 16: site visit to provide recruitment training (one site)</li> <li>• Month 17: site visits to provide recruitment training (two sites)</li> <li>• Month 22: site visits to provide recruitment training (two sites)</li> <li>• Month 22: 'Tips and Guidance' document circulated to all sites</li> </ul>
<b>RCT5</b>	<p>1) Complex recruitment pathways (from point of identifying eligible patients, to the recruitment appointment)</p> <p>2) Discomfort approaching the full spectrum of eligible patients (equipoise difficulties).</p> <p>3) Difficulties conveying equipoise during recruitment appointments (when describing trial arms)</p> <p>4) Tendency to accept patient preferences, without exploration</p>	<ul style="list-style-type: none"> <li>• Month 6: Site-specific group feedback delivered to Sites 1 and 2</li> <li>• Month 6: Individual feedback provided to recruiters in Sites 1 and 2.</li> <li>• Month 7: Adapted 'Tips and Guidance' document sent to Site 3.</li> <li>• Month 9: Individual feedback to recruiter in Site 2.</li> <li>• Month 10: Visit to Site 2 to provide training for new recruiters</li> </ul>

Figure 1: Timeline of RCTs, with points of QRI integration and point at which QRI-actions were implemented

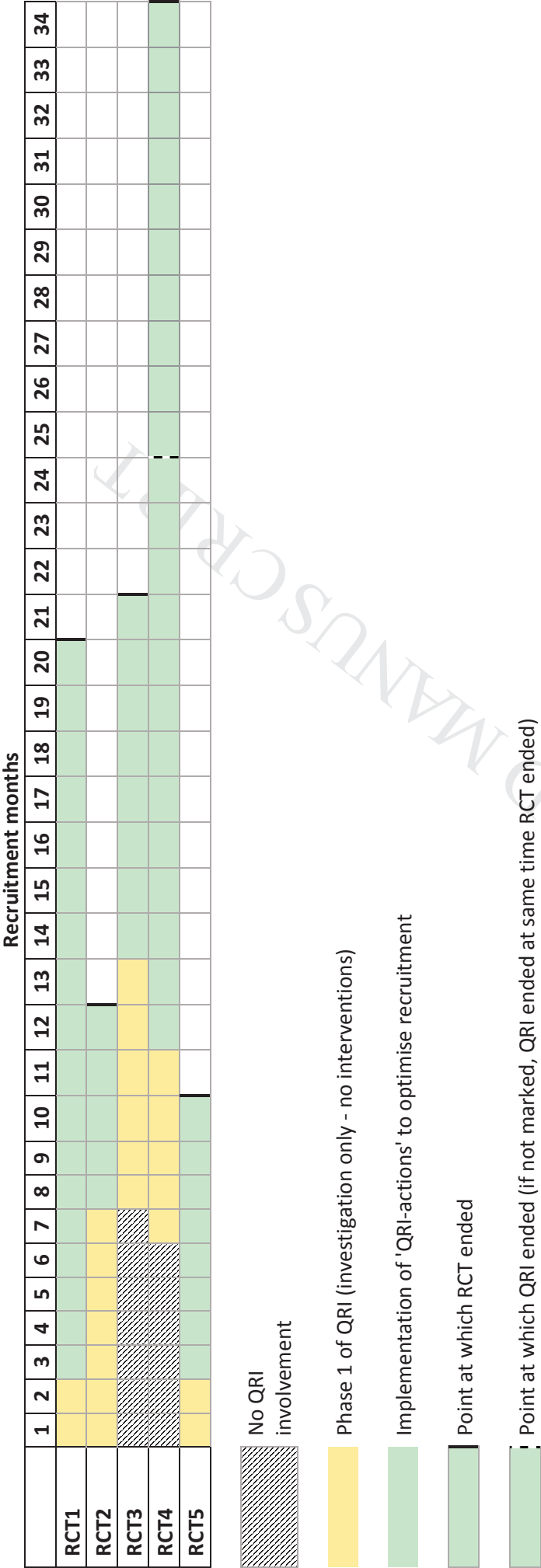
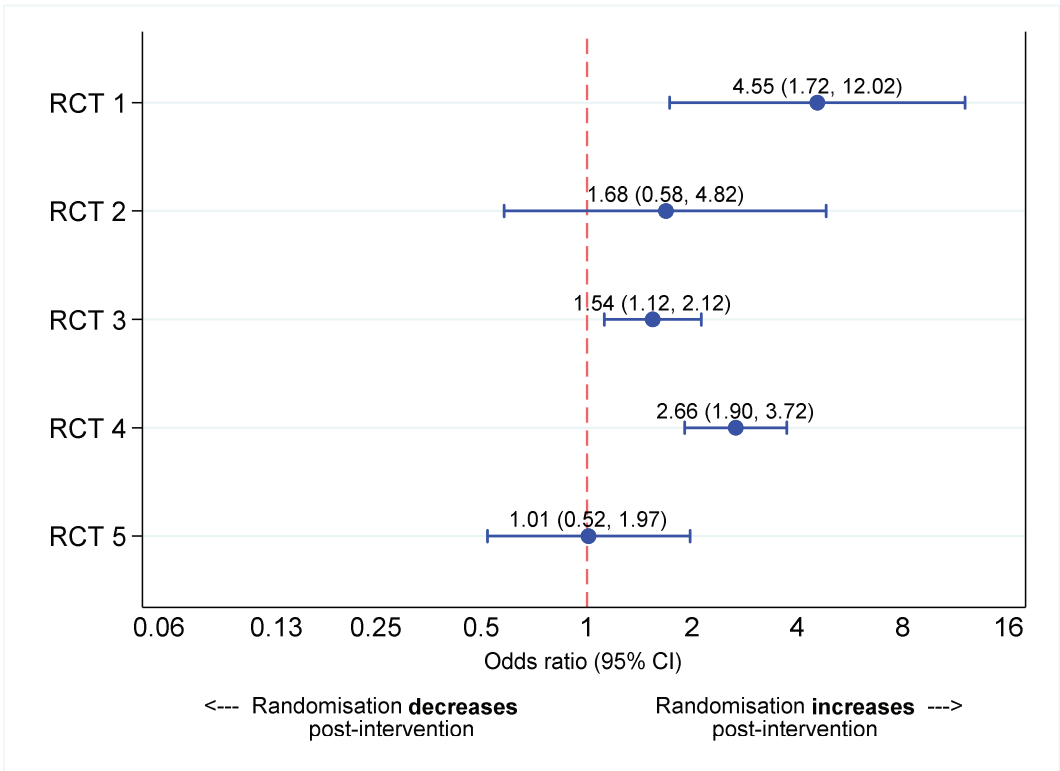


Figure 2: Results of Analysis 1 (change in randomisation success, pre and post intervention) and Analysis 2 (changes in numbers of patients approached, pre and post intervention)

Panel 1: Odds ratio of randomisation success after the first QRI-action, shown for individual trials



Panel 2: Incident rate ratios (IRR) of eligible and approached (E&A) patients after the first QRI-action, shown for individual trials

